preparation from testicular carcinomas. Thus, the PTO concludes, "similarity between both markers would allow for cross-reactivity of the antibodies." Office Action, pg. 3. Applicants respectfully disagree.

Evidence that the antigens of GCTM-2 and GCTM-5 have distinct patterns of tissue expression is provided in the accompanying Declaration of Martin Frederick Pera Under 37 C.F.R. § 1.132 ("Second Pera Declaration"). The Second Pera Declaration provides experimental data which show that the antigen recognized by the GCTM-5 antibody of the present invention is biochemically distinct from the antigens recognized by the GCTM-1, -2, -3, and -4 antibodies. Second Pera Declaration ¶ 4.

Specifically, Figure 1 of the Second Pera Declaration shows an immunoblot of GCTM-5 antigen affinity purified from a CFPAC-1 pancreatic adenocarcinoma cell line condition media ("CM") (*see* Second Pera Declaration, Figure 1, panel C: lane 1, untreated CM; lane 2, N-Glycanase (PNGase F) treated CM; lane 3, sialidase A treated CM; lane 4, O-Glycanase treated CM; lane 5, CM treated with all three enzymes). Second Pera Declaration ¶ 5. The data illustrated in Figure 1C of the Second Pera Declaration demonstrate that sialidase treatment destroys GCTM-5 reactivity. *Id.* By contrast, previous studies have shown that GCTM-2 antibodies bind to an antigen that is not sialidase sensitive. *Id.* In fact, independent studies have shown clearly that sialidase treatment enhances the reactivity of GCTM-2 antibodies with its epitope (*see* Second Pera Declaration, Exhibit 1 (Cooper et al., "Biochemical Properties of a Keratan Sulphate/Chondroitin Sulphate Proteoglycan Expressed in Primate Pluripotent Stem Cells," *J. Anat.* 200:259-265 (2002)). *Id.* Thus, the antigen identified and bound by the GCTM-5 antibody of the present invention must be biochemically distinct from the antigen identified and bound by the GCTM-2 antibody of Schopperle. *Id.*

Table 1 of the Second Pera Declaration illustrates the reactivity of the GCTM-5 antibody of the present invention in normal and pathological human tissues. Second Pera Declaration ¶ 6. The data show that the GCTM-5 antibody has distinct patterns of tissue expression that are clearly different to those of the GCTM-2 antibodies of Schopperle. *Id.* For instance, GCTM-2 antibodies stain the surface of undifferentiated embryonal carcinoma stem cells and undifferentiated embryonic stem cells, whereas the GCTM-5 antibodies of the present invention react only with a minority population of differentiating cells. *Id*; *see also* present application, Table 1 (p. 32). This is also described in Stamp et al., "A Novel Cell-Surface

Marker Found on Human Embryonic Hepatoblasts and a Subpopulation of Hepatic Biliary Epithelial Cells," *Stem Cells* 23:103-112 (2005) ("Stamp") (attached hereto as Exhibit A) at page 102 (Table 1).

As further evidence for the distinct pattern of reactivity of GCTM-2 antibodies compared to the GCTM-5 antibodies of the present invention, Figure 2 of the Second Pera Declaration illustrates the reactivity of the GCTM-5 antibodies of the present invention to fetal thymus and fetal pancreatic ductiles. Second Pera Declaration ¶ 8. This pattern of reactivity is clearly different to that of GCTM-2 antibodies, which do not react with fetal thymus or pancreas (*see* Second Pera Declaration, Exhibit 2 (Mason and Pera, "Immunohistochemical and Biochemical Characterisation of the Expression of a Human Embryonal Carcinoma Cell Proteoglycan Antigen in Human Germ Cell Tumours and other Tissues," *Eur. J. Cancer* 28A(617):1090-1098 (1992))). *Id.*

In addition to the foregoing, applicants respectfully submit that the rejection over Schopperle is based on the PTO's erroneous assertion that the GCTM-2 monoclonal antibody taught by Schopperle was derived from membrane preparations of testicular carcinoma cells and would therefore cross-react with the epitope recognized by the GCTM-5 antibody of the present invention. Yet, the sources of antigens used to generate the antibodies in question represent two completely different tumor cell types that display distinct histology, biological behavior, and gene expression patterns. For instance, the GCTM-5 antibody of the present invention was raised against a membrane preparation from a testicular seminoma. *See* present application, p. 29, ll. 7-21; *see also* Stamp p. 104, 2nd col., 3rd para., 11. 1-3. By contrast, the GCTM-2 antibody of Schopperle was raised against embryonal carcinoma cell extracts. *See* Schopperle, Abstract.

Moreover, Schopperle clearly states that the GCTM-2 antibody described therein preferentially binds to an epitope expressed on the surface of *nonseminomatous* cells (*see* Schopperle, p. 285, 2nd col., 1st full para., ll. 1-8), as opposed to the GCTM-5 antibody of the present invention, which was generated by immunization with a membrane preparation of *seminomatous* cells.

Further, the antibody described in Schopperle binds to a 200 kDa glycoprotein (*see, e.g.*, Schopperle, p. 286, Results and Discussion; Figures 1 and 3), a characteristic shared by other cell markers, including TRA-1-60, TRA-1-81, K-21, and K-4 (*see* Schopperle, p. 288,

2nd column, 1st full paragraph, ll. 1-5). By contrast, the GCTM-5 antibody of the present invention binds to a 50 kDa protein (*see*, *e.g.*, present application, Figure 2; p. 34, ll. 10-20).

For all of these reasons, it cannot be asserted that Schopperle teaches or suggests each and every limitation of the claims. Therefore, the anticipation rejection based on Schopperle is improper and should be withdrawn.

The rejection of claims 109-113 and 115-121 under 35 U.S.C. § 102(b) as anticipated by Pera et al., "Analysis of Cell-Differentiation Lineage in Human Teratomas Using New Monoclonal Antibodies to Cytostructural Antigens of Embryonal Carcinoma Cells," *Differentiation* 39:139-149 (1988) ("Pera I") is respectfully traversed.

Pera I produced monoclonal antibodies to cytostructurally associated antigens of human embryonal carcinoma cells. Monoclonal antibody *GCTM-1* stained the nuclei of all human cells tested and served as a positive control. This antibody immunoprecipitated proteins of 85 and 66 k Da from human embryonal carcinoma cells. *GCTM-2* recognized an epitope on a 200-k Da extracellular protein present on the surface of embryonal carcinoma cells. Antibody *GCTM-3* bound to a 57-k Da cytoskeletal protein expressed in human embryonal carcinoma. Antibody *GCTM-4* recognized a determinant present on a 69-k Da polypeptide, associated with a component of the lysosomal compartment, which was expressed in embryonal carcinoma cells, but no other cell type tested.

The PTO asserts that while Pera I is silent with respect to the antibodies binding to a stem cell marker characterized by binding to a GCTM-5 antibody, the antibodies disclosed in Pera I recognized antigens derived from membrane preparation from a testicular carcinoma with similar apparent molecular weight. According to the PTO, similarity between markers would allow for cross-reactivity of the antibodies. Applicants respectfully disagree.

The PTO's rejection here is maintained on the erroneous assertion that the antibodies of Pera I were generated from membrane preparations of testicular carcinoma cells and would therefore bind to epitopes of similar molecular weights to those identified by the GCTM-5 antibody of the present invention. However, the GCTM-1, -3, and -4 antibodies of Pera I were raised against embryonal carcinoma cell extracts, whereas the GCTM-5 antibody of the present invention was prepared and raised against a membrane preparation of testicular seminoma. In any event, the GCTM-5 antibody of the present invention recognizes a cell surface protein with limited patterns of tissue expression. *See* Second Pera Declaration ¶ 6. This

is in stark contrast to the GCTM-1, -3, and -4 antibodies of Pera I. For instance, GCTM-1 antibodies only recognize a nuclear antigen expressed in human cells, GCTM-3 antibodies only recognize a cytoskeletal antigen present in GCT-4 yolk sac carcinoma cells, and GCTM-4 antibodies recognize a lysosomal protein. Thus, the GCTM-1, -3, and -4 epitopes are located at completely different cellular compartments to the epitope identified by the GCTM-5 antibody of the present invention.

Since Pera I fails to teach or suggest each and every limitation of the claims, the anticipation rejection based on this reference is improper and should be withdrawn.

The rejection of claims 109-113 and 115-121 under 35 U.S.C. § 102(e) as anticipated by PCT Publication No. WO 03/040355 to Pera et al. ("Pera II") or PCT Publication No. WO 01/98463 to Pera et al. ("Pera III") is respectfully traversed.

Pera II and Pera III disclose various monoclonal antibodies.

While the Examiner acknowledges that Pera II and Pera III do not explicitly describe an antibody to GCTM-5, it is alleged the antibodies disclosed in these documents would cross-react with the epitope recognized by the GCTM-5 antibody of the present invention. Again, applicants respectfully disagree.

The antibodies disclosed in Pera II and Pera III bind to the same protein that is recognized by GCTM-2 antibodies of Schopperle, as discussed *supra*. Accordingly, for the reasons noted above (and provided in the Second Pera Declaration), the GCTM-2 protein is clearly biochemically distinct from the protein recognized by the GCTM-5 antibody of the present invention. Moreover, the antibody described in Pera III binds to a 200 kDa glycoprotein, whereas the other molecular weight proteins cited by the PTO (*i.e.*, being 68 to 85 kDa) are non-GCTM-markers. *See, e.g.*, Pera III pp. 17-18.

Since Pera II and Pera III fail to teach or suggest each and every limitation of the claims, the anticipation rejection based on these references is improper and should be withdrawn.

The rejection of claims 170-175 and 177-181 under 35 U.S.C. § 103(a) for obviousness over Schopperle, Pera I, Pera II, and Pera III, each in view of U.S. Patent No. 4,281,061 to Zuk et al. ("Zuk") is respectfully traversed.

Zuk is cited for teaching that reagents or pharmaceutical compositions can be provided as kits as a matter of convenience, optimization, and economy of the user.

According to the PTO, it would have been obvious for a person of ordinary skill in the art at the time of the invention to apply the teachings of Zuk to those of Schopperle, Pera I, Pera II, or Pera III to obtain a kit comprising a detector of a cell type which identifies on the cell type a cell marker, characterized by binding to a GCTM-5 antibody, as recited in the present claims.

However, Zuk does not overcome the above-noted deficiencies of Schopperle, Pera I, Pera II, and Pera III. Therefore, this rejection is improper and should be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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Exhibit A: Stamp et al., "A Novel Cell-Surface Marker Found on Human Embryonic Hepatoblasts and a Subpopulation of Hepatic Biliary Epithelial Cells," Stem Cells 23:103-112 (2005)